EXHIBIT A
MARKED UP VERSION OF AMENDED SPECIFICATION

Page 49, line 22:

--A number of additional methods for producing nucleic acids and polypeptides are known in the art~~, and the methods can be used to produce polypeptides having specificity for h2520-109~~. *See* for example, Roberts *et al., Proc. Natl. Acad. Sci U.S.A., 94*:12297-12303, 1997, which describes the production of fusion proteins between an mRNA and its encoded peptide. See also Roberts, R., *Curr. Opin. Chem. Biol., 3*:268-273, 1999. Additionally, U.S. Patent No. 5,824,469 describes methods of obtaining oligonucleotides capable of carrying out a specific biological function. The procedure involves generating a heterogeneous pool of oligonucleotides, each having a 5' randomized sequence, a central preselected sequence, and a 3' randomized sequence. The resulting heterogeneous pool is introduced into a population of cells that do not exhibit the desired biological function. Subpopulations of the cells are then screened for those which exhibit a predetermined biological function. From that subpopulation, oligonucleotides capable of carrying out the desired biological function are isolated.--

Page 50, line 23:

--Chemically modified derivatives of ~~the h2520-109~~ polypeptides may be prepared by one skilled in the art, given the disclosures set forth herein below. ~~h2520-109 polypeptide~~ Polypeptide derivatives are modified in a manner that is different, either in the type or location of the molecules naturally attached to the polypeptide. Derivatives may include molecules formed by the deletion of one or more naturally-attached chemical groups. The polypeptide comprising the amino acid sequence of SEQ ID NO: 2, or a ~~h2520-109~~ polypeptide variant, may be modified by the covalent attachment of one or more polymers. For example, the polymer selected is typically water soluble so that the protein to which it is attached does not precipitate in an aqueous environment, such as a physiological environment. Included within the scope of suitable polymers is a mixture of polymers. Preferably, for therapeutic use of the end-product preparation, the polymer will be pharmaceutically acceptable.--

Page 51, line 1:

--The polymers each may be of any molecular weight and may be branched or unbranched. The polymers each typically have an average molecular weight of between about 2 kDa to about 100 kDa (the term "about" indicating that in preparations of a water soluble polymer, some molecules will weigh more, some less, than the stated molecular weight). The average molecular weight of each polymer is preferably between about 5 kDa and about 50 kDa, more preferably between about 12 kDa and about 40 kDa and most preferably between about 20 kDa to about 35

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kDa. Suitable water soluble polymers or mixtures thereof include, but are not limited to, N-linked or O-linked carbohydrates; sugars; phosphates; polyethylene glycol (PEG) (including the forms of PEG that have been used to derivatize proteins, including mono-(C1-C10) alkoxy-or aryloxy-polyethylene glycol), monomethoxy-polyethylene glycol; dextran (such as low molecular weight dextran of, for example about 6 kD;, cellulose, or other carbohydrate- based polymers, poly-(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (*e.g.*, glycerol) and polyvinyl alcohol. Also encompassed by the present invention are bifunctional crosslinking molecules which may be used to prepare covalently attached multimers of the polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or a ~~h2520-109~~ polypeptide variant.--

Page 51, line 19:

--In general, chemical derivatization may be performed under any suitable condition used to react a protein with an activated polymer molecule. Methods for preparing chemical derivatives of polypeptides will generally comprise the steps of (a) reacting the polypeptide with the activated polymer molecule (such as a reactive ester or aldehyde derivative of the polymer molecule) under conditions whereby the polypeptide comprising the amino acid sequence of SEQ ID NO: 2, or a ~~h2520-109~~ polypeptide variant becomes attached to one or more polymer molecules, and (b) obtaining the reaction product(s). The optimal reaction conditions will be determined based on known parameters and the desired result. For example, the larger the ratio of polymer molecules:protein, the greater the percentage of attached polymer molecule. In one embodiment, the ~~h2520-109~~ polypeptide derivative may have a single polymer molecule moiety at the amino terminus. (*See*, for example, U.S. Patent No. 5,234,784). The pegylation of the polypeptide may be specifically carried out by any of the pegylation reactions known in the art, as described for example in the following references: Francis *et al., Focus on Growth Factors, 3*:4-10 (1992); EP 0154316; EP 0401384 and U.S. Patent No. 4,179,337. For example, pegylation may be carried out via an acylation reaction or an alkylation reaction with a reactive polyethylene glycol molecule (or an analogous reactive water-soluble polymer) as described herein. For the acylation reactions, the polymer(s) selected should have a single reactive ester group. For reductive alkylation, the polymer(s) selected should have a single reactive aldehyde group. A reactive aldehyde is, for example, polyethylene glycol propionaldehyde, which is water stable, or mono C1-C10 alkoxy or aryloxy derivatives thereof (see U.S. Patent No. 5,252,714).--

Page 52, line 8:

--In another embodiment, ~~h2520-109~~ polypeptides may be chemically coupled to biotin, and the biotin/~~h2520-109~~ polypeptide molecules which are conjugated are then allowed to bind to avidin, resulting in tetravalent

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avidin/biotin/polypeptide molecules. ~~h2520-109 polypeptides~~ Polypeptides may also be covalently coupled to dinitrophenol (DNP) or trinitrophenol (TNP) and the resulting conjugates precipitated with anti-DNP or anti-TNP-IgM to form decameric conjugates with a valency of 10.--

Page 52, line 14:

--Generally, conditions which may be alleviated or modulated by the administration of the present ~~h2520-109~~ polypeptide derivatives include those described herein for ~~h2520-109~~ polypeptides. However, the ~~h2520-109~~ polypeptide derivatives disclosed herein may have additional activities, enhanced or reduced biological activity, or other characteristics, such as increased or decreased half-life, as compared to the non-derivatized molecules.--

Page 55, line 33:

--The selective binding agents, including ~~anti-h2520-109~~ antibodies, are also useful for *in vivo* imaging. An antibody labeled with a detectable moiety may be administered to an animal, preferably into the bloodstream, and the presence and location of the labeled antibody in the host is assayed. The antibody may be labeled with any moiety that is detectable in an animal, whether by nuclear magnetic resonance, radiology, or other detection means known in the art.--

Page 56, line 5:

--Selective binding agents of the invention, including ~~anti-h2520-109~~ antibodies, may be used as therapeutics. These therapeutic agents are generally agonists or antagonists, in that they either enhance or reduce, respectively, at least one of the biological activities of a ~~h2520-109~~ polypeptide. In one embodiment, antagonist antibodies of the invention are antibodies or binding fragments thereof which are capable of specifically binding to a ~~h2520-109~~ polypeptide and which are capable of inhibiting or eliminating the functional activity of a ~~h2520-109~~ polypeptide *in vivo* or *in vitro*. In preferred embodiments, the selective binding agent, *e.g.*, an antagonist antibody will inhibit the functional activity of a ~~h2520-109~~ polypeptide by at least about 50%, and preferably by at least about 80%. In another embodiment, the selective binging agent may be an antibody that is capable of interacting with a ~~h2520-109~~ binding partner (a ligand, co-factor, or receptor) thereby inhibiting or eliminating ~~h2520-109~~ activity *in vitro* or *in vivo*. Selective binding agents, including agonist and antagonist ~~anti-h2520-109~~ antibodies are identified by screening assays which are well known in the art.--

Page 58, line 4:

--This high throughput expression profiling has a broad range of applications with respect to the ~~h2520-109~~ molecules of the invention, including, but not limited to: the identification and validation of ~~h2520-109~~ disease-related genes as targets for therapeutics; molecular toxicology of ~~h2520-109~~ molecules and inhibitors thereof; stratification of populations and generation of surrogate markers for clinical trials; and the enhancement of a ~~an h2520-109~~ related small molecule drug discovery by aiding in the identification of selective compounds in high throughput screens (HTS).--

Page 59, line 22:

--Once a set of test molecules has been identified as interacting with a ~~h2520-109~~ polypeptide, the molecules may be further evaluated for their ability to increase or decrease ~~h2520-109~~ polypeptide activity. The measurement of the interaction of test molecules with ~~h2520-109~~ polypeptides may be carried out in several formats, including cell-based binding assays, membrane binding assays, solution-phase assays and immunoassays. In general, test molecules are incubated with a ~~h2520-109~~ polypeptide for a specified period of time, and ~~h2520-109~~ polypeptide activity is determined by one or more assays for measuring biological activity.--

Page 59, line 30:

--The interaction of test molecules with ~~h2520-109~~ polypeptides may also be assayed directly using polyclonal or monoclonal antibodies in an immunoassay. Alternatively, modified forms of ~~h2520-109~~ polypeptides containing epitope tags as described herein may be used in immunoassays.--

Page 60, line 1:

--In the event that ~~h2520-109~~ polypeptides display biological activity through an interaction with a binding partner (*e.g.*, a receptor, a ligand or a co-factor), a variety of in vitro assays may be used to measure the binding of a ~~h2520-109~~ polypeptide to the corresponding binding partner (such as a selective binding agent, receptor, ligand, or co-factor). These assays may be used to screen test molecules for their ability to increase or decrease the rate and/or the extent of binding of a ~~h2520-109~~ polypeptide to its binding partner. In one assay, a ~~h2520-109~~ polypeptide is immobilized in the wells of a microtiter plate. Radiolabeled ~~h2520-109~~ binding partner (for example, iodinated ~~h2520-109~~ binding partner) and the test molecule(s) can then be added either one at a time (in either order) or simultaneously to the wells. After incubation, the wells can be washed and counted using a scintillation counter,

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for radioactivity to determine the extent to which the binding partner bound to ~~h2520-109~~ polypeptide. Typically, the molecules will be tested over a range of concentrations, and a series of control wells lacking one or more elements of the test assays can be used for accuracy in the evaluation of the results. An alternative to this method involves reversing the "positions" of the proteins, *i.e.*, immobilizing ~~h2520-109~~ binding partner to the microtiter plate wells, incubating with the test molecule and radiolabeled ~~h2520-109~~ polypeptide, and determining the extent of ~~h2520-109~~ polypeptide binding. See, for example, Chapter 18, *Current Protocols in Molecular Biology*, Ausubel *et al.*, eds., John Wiley & Sons, New York, NY (1995).--

Page 60, line 21:

--As an alternative to radiolabelling, a ~~h2520-109~~ polypeptide or its binding partner may be conjugated to biotin and the presence of biotinylated protein can then be detected using streptavidin linked to an enzyme, such as horseradish peroxidase (HRP) or alkaline phosphatase (AP), that can be detected colorometrically, or by fluorescent tagging of streptavidin. An antibody directed to a ~~h2520-109~~ polypeptide or to a ~~h2520-109~~ binding partner and conjugated to biotin may also be used and can be detected after incubation with enzyme-linked streptavidin linked to AP or HRP.--

Page 60, line 28:

--A ~~h2520-109~~ polypeptide or a ~~h2520-109~~ like binding partner can also be immobilized by attachment to agarose beads, acrylic beads or other types of such inert solid phase substrates. The substrate-protein complex can be placed in a solution containing the complementary protein and the test compound. After incubation, the beads can be precipitated by centrifugation, and the amount of binding between a ~~h2520-109~~ polypeptide and its binding partner can be assessed using the methods described herein. Alternatively, the substrate-protein complex can be immobilized in a column, and the test molecule and complementary protein are passed through the column. The formation of a complex between a ~~h2520-109~~ polypeptide and its binding partner can then be assessed using any of the techniques set forth herein, *i.e.*, radiolabelling, antibody binding or the like.--

Page 61, line 5:

--Another *in vitro* assay that is useful for identifying a test molecule which increases or decreases the formation of a complex between a ~~h2520-109~~ polypeptide and a ~~h2520-109~~ binding partner is a surface plasmon resonance detector system such as the BIAcore assay system (Pharmacia, Piscataway, NJ). The BIAcore system may be carried out using the manufacturer's protocol. This assay essentially

involves the covalent binding of either ~~h2520-109~~ polypeptide or a ~~h2520-109~~ binding partner to a dextran-coated sensor chip which is located in a detector. The test compound and the other complementary protein can then be injected, either simultaneously or sequentially, into the chamber containing the sensor chip. The amount of complementary protein that binds can be assessed based on the change in molecular mass which is physically associated with the dextran-coated side of the sensor chip; the change in molecular mass can be measured by the detector system.--

Page 61, line 17:

--In some cases, it may be desirable to evaluate two or more test compounds together for their ability to increase or decrease the formation of a complex between a ~~h2520-109~~ polypeptide and a ~~h2520-109~~ binding partner. In these cases, the assays set forth herein can be readily modified by adding such additional test compound(s) either simultaneous with, or subsequent to, the first test compound. The remainder of the steps in the assay are set forth herein.--

Page 61, line 23:

--*In vitro* assays such as those described herein may be used advantageously to screen large numbers of compounds for effects on complex formation by ~~h2520-109~~ polypeptide and ~~h2520-109~~ binding partner. The assays may be automated to screen compounds generated in phage display, synthetic peptide, and chemical synthesis libraries.--

Page 61, line 28:

--Compounds which increase or decrease the formation of a complex between a ~~h2520-109~~ polypeptide and a ~~h2520-109~~ binding partner may also be screened in cell culture using cells and cell lines expressing either ~~h2520-109~~ polypeptide or ~~h2520-109~~ binding partner. Cells and cell lines may be obtained from any mammal, but preferably will be from human or other primate, canine, or rodent sources. The binding of a ~~h2520-109~~ polypeptide to cells expressing ~~h2520-109~~ binding partner at the surface is evaluated in the presence or absence of test molecules, and the extent of binding may be determined by, for example, flow cytometry using a biotinylated antibody to a ~~h2520-109~~ binding partner. Cell culture assays can be used advantageously to further evaluate compounds that score positive in protein binding assays described herein.--

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Page 74, line 27:

--An effective amount of a ~~h2520-109~~ pharmaceutical composition to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon the molecule delivered, the indication for which the ~~h2520-109~~ molecule is being used, the route of administration, and the size (body weight, body surface or organ size) and condition (the age and general health) of the patient. Accordingly, the clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about 0.1 mg/kg to up to about 100 mg/kg or more, depending on the factors mentioned above. In other embodiments, the dosage may range from 0.1 mg/kg up to about 100 mg/kg; or 1 mg/kg up to about 100mg/kg; or 5 mg/kg up to about 100 mg/kg.--

Page 75, line 4:

--The frequency of dosing will depend upon the pharmacokinetic parameters of the ~~h2520-109~~ molecule in the formulation used. Typically, a clinician will administer the composition until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via implantation device or catheter.--

Page 96, line 25:

--A BLAST search of the Celera Human Genome database was conducted using the huE3αI cDNA sequence (SEQ ID NO: 1) as a probe. The sequences identified in the search were used to manually assemble a polynucleotide sequence (SEQ ID NO: 18) which was discovered to have a single nucleotide mismatch at nucleotide 4657, corresponding to nucleotide 5397 of the huE3αI cDNA sequence (SEQ ID NO: 1). The polynucleotide sequence of SEQ ID NO: 18 contains a huE3αI SNP with a change of a ~~cytosine~~ thymidine to a ~~thymidine~~ cytosine at position ~~4702~~ 4657, which caused a change in the ~~predicted~~ amino acid sequence of SEQ ID NO: ~~2~~ 19 at position 1573 to change from a Trp residue to an Arg residue ~~to a W (Trp) residue at position 1508~~ (corresponding to the Trp residue at position 1568 in SEQ ID NO: 2).--

Page 97, line 9:

--These experiments have confirmed the sequence of a huE3αI SNP set out in SEQ ID NO: ~~17~~ 18 wherein the nucleotide at position ~~4702~~ 4657 is a

~~thymidine~~ cytosine. Accordingly, the correct predicted amino acid sequence for this huE3αI SNP is set out as SEQ ID NO: 19, wherein the residue at position ~~1568~~ 1573 is ~~W (Trp)~~ Arg.--